Henkel Position

Alternatives to animal testing

Contents

Our commitment

Safety and compatibility of all Henkel products

Henkel is responsible for safety, health and environmental matters relating to the production, distribution and use of its products. Customers and consumers can be sure that Henkel products are safe when used as intended and have been extensively assessed for compatibility with human health and the environment.

Our teams of experts, composed of product developers and product safety specialists, begin systematically evaluating new products as early as in the research and development phase to determine whether they could pose a hazard to human health or the environment. Before they ultimately reach the market, the ingredients and the finished products themselves are also subjected to numerous tests and assessments. Many of these are legally required. Above and beyond this, our own additional in-house standards are designed to ensure that our products have a high level of safety for customers, consumers, and the environment.

Implementation of product safety

The business sectors are responsible for the implementation of product safety. Regular audits are carried out to verify compliance with corporate product safety requirements and procedures.

Wherever possible, we demonstrate the safety through existing data or through accepted alternative test methods, thus avoiding animal testing. Henkel only ever uses such type of test if legislation so provides and no accepted alternative test methods are available for obtaining the necessary safety data.

Naturally, at the same time, we comply with legal regulations that do not allow animal testing, e.g. testing in order to meet the requirements of the EU legislation on cosmetics.

Selected non-animal screening and alternative methods used in Henkel laboratories:

- *Indicator assays for determining cytotoxic effects*
- *Organotypical skin models for studying irritation of the skin*
- *Hen's egg test for mucous membrane compatibility (Hen's Egg Test on the Chorionallantoic Membrane, HET-CAM Test)*
- *Hen's egg test for determining mutagenic properties (Hen's Egg Test for Micronucleus Formation, HET-MN Test)*
- *Testing of skin absorption (OECD 428)*
- *Photohemolysis test for determining phototoxic potential*
- *Dendritic cells for determining sensitizing potential*
- *In-silico methods: quantitative structure-activity relationships using chemical informatics systems*

We would very much like to be able today to answer all questions about the safety of our products and the ingredients we use without any animal testing at all. However, we are obliged to use methods that have been accepted by the legislators. Alternative methods are not yet available for all safety aspects, so that it is unfortunately not possible today to avoid animal testing completely. Such testing can only be eliminated completely when accepted alternative methods are available for all categories of animal tests.

Developing test methods that replace animal testing and making these test methods generally available is a top priority at Henkel. Having been active in this field since 1980, we considerably intensified and pooled our research efforts concerning alternative methods in 2006. Here, an interdisciplinary team of experts works to develop alternative test methods that are needed worldwide. At Henkel, these research capabilities are supported by expert knowledge of the effects of ingredients and products on skin and hair.

Accepted alternative test methods:

For some of the legally required tests there are already scientifically validated alternative methods that have been accepted by the legislators:

- Tests for skin-corrosive properties (OECD 430, 431 and 435)
- Tests for skin-irritant properties (OECD 439)
- Tests for acute phototoxicity or irritation (OECD 432)
- Tests for eye corrosion / severe eye irritation (OECD 437, 438 and 460). These are not, however, full replacements as they do not cover the entire spectrum of possible effects.
- Tests for skin absorption (OECD 428)
- *In-vitro* tests for mutagenic properties (OECD 487, 471, 473, 476, and others)
- Tests for acute fish toxicity (OECD 126)

Our responsibility

Toward humans, animals and the environment

As long as safety data obtained from animal testing are indispensable for an intended purpose, Henkel will take precautions to ensure that the number of tests is kept to a minimum.

The following aspects in particular are carefully examined before commissioning any tests:

- What are the legal requirements for ingredients or products?
- Are applicable safety data available for the intended purpose?
- Are alternatives to animal testing available and can they be used for safety assessments?

If these checks reveal that an animal test cannot be avoided, we ensure that the **3Rs principle** will be applied. The 3Rs stand for replace, reduce and refine. They relate both to the development of test methods and the use of animal testing.

- **"Replace"** is Henkel's goal: to develop and use alternative test methods which will ultimately replace animal testing altogether.
- **"Reduce"**: to reduce the number of animals used in tests. This is achieved by carrying out testing systematically and referring to already existing information.
- **"Refine"**: to optimize the tests so that test animals are subjected to a minimum of stress, until such time as the tests can be replaced.

Henkel itself does not carry out any animal testing. Before commissioning any necessary tests by an audited external research institute, we always check whether the institute can carry out these tests in a manner that complies with all legal requirements and is in line with our commitment and responsibility. The key criteria are conformity with recognized protocols, such as the test guidelines of the Organisation for Economic Co-operation and Development (OECD) and the principles of good laboratory practice (GLP), and with the standards and country-specific regulations referred to in the EU Directive on the Protection of Animals.

Our goal

Alternative test methods for all safety aspects

The aim of replacing animal testing altogether by alternative test methods has been of prime importance to us for some thirty years.

We began working on the development of such methods as far back as 1980, both internally through our research and product safety departments and in cooperation with external research institutions.

Although these efforts have produced a number of successful results, a great deal still needs to be done before it will be possible to eliminate animal testing completely. Among other possible options, this will involve consistent use of the most advanced research methods in the areas of molecular biology and computer technologies.

Building on the in vitro Phenion® full thickness skin model and other such non-animal testing approaches, we intend to develop further new alternative methods.

The Phenion® Full Thickness Skin Model:

This robust full thickness skin model developed by Henkel is based on human cells. It can be produced to a constant and very high level of quality for use in the laboratory. A test substance is applied to the Phenion® Full Thickness Skin Model so that its effect on the skin tissue can be systematically evaluated. The substance, e.g. a cream formulation, is applied topically using a brush to the skin model over a defined period of time. In this way, the effect of the substance on the cell layers in the skin can be studied.

Henkel is also working with partners on an “Open Source Reconstructed Epidermis Model” (OS-REp) to determine skin-irritating effects. Knowledge of this model – from its production to its uses – will be made generally available so that others can use it as a replacement for animal testing. The documentation has been submitted to EURL ECVAM, the European Union Reference Laboratory for alternatives to animal testing, which is responsible for scientifically validating alternative methods. We hope that this model will soon be able to establish itself as a “gold standard”.

The Local Lymph Node Assay (LLNA), which was approved in 2004 by the OECD as a test for skin-sensitizing properties and has been used in a revised version (OECD 429) since 2010, makes an important contribution to refinement and reduction. The number of animals needed for certain tests was also reduced by the harmonization of test requirements and the development of new test methods, such as the Acute Toxic Class Method (OECD 423) and the Fixed Dose Method (OECD 420) for testing for acute oral toxicity. Regarding reproduction toxicology, the Extended One Generation Study (OECD 443) can

also help reduce the number of animals. The industry played a decisive role in the development of all these test protocols.

Further methods, e.g. for the evaluation of skin-sensitizing properties, are in the validation phase (see http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam).

Steps to achieve our goal

Scientific approaches

Important approaches pursued by our experts include:

- the development of *in-vitro* (Latin for "in glass") methods based on biological materials (for example, skin or other human body cells) that will be suitable for reliably verifying the safety and compatibility of product ingredients;
- the development of *in-silico* (Latin neologism for "in the computer") methods to determine the compatibility of substances on the basis of their chemical structure;
- the development of testing and evaluation strategies which efficiently combine and use information from different sources.

In-vitro methods:

As an alternative to animal testing, cell and tissue cultures can be used in certain cases to test product ingredients. Cell culture experiments can show, for example, the lowest concentration at which an ingredient can influence the vitality and function of cells. The results enable conclusions to be drawn about the ingredient's compatibility with tissue. Cell cultures are now also used routinely to test substances for mutagenic properties. Tissue cultures are additionally used to test substances for compatibility with the skin and mucous membranes as well as for possible irritant effects on the skin and eyes.

In-silico methods:

Substances with similar chemical structures often have similar properties. In these cases, knowledge of the properties of a few representative substances may be sufficient to be able to deduce the properties of a series of similar substances. By analogy, certain properties of these representative substances can also be assumed to be properties of the other substances in the series. Specially developed computer programs help the experts to perform such evaluations. It is anticipated that combinations of such computations will make it possible in the future to narrow down the number of substances to be tested. Generally, these selected substances will then have to be tested according to the legally required test methods.

One important result of the research conducted so far into approaches to replace animal testing is the incorporation of a range of new cell and tissue culture systems into the repertoire of alternative methods. The majority of these methods are used to investigate the behavior of a substance in the body or its effect on skin and mucous membranes. A single-layer epidermis skin model was included in the OECD guidelines some time ago as a method for testing substances for skin-corrosive properties (see "Accepted alternative test methods" box). Following this, a similar skin model was accepted by the then

European Centre for the Validation of Alternative Methods (ECVAM, now EURL ECVAM, the European Union Reference Laboratory for alternatives to animal testing) and by the OECD for testing for irritating properties. Official acceptance was also recently accorded to alternative methods for determining effects harmful to the eyes.

Since individual alternative methods often cannot completely replace a particular animal test, the appropriate combination of data from different methods and data sources is becoming increasingly important.

Henkel and other companies and institutions are working intensively to develop additional valid alternative methods and integrated test strategies for reducing animal testing.

Official acceptance

When an alternative method is developed, it must undergo an internationally recognized scientific validation process before being officially accepted. This procedure is very complicated and usually takes more than ten years.
An alternative method that has been developed must first be subjected to comparative experiments in a number of laboratories (round-robin studies) to demonstrate that the results obtained carry as much weight as those of *in-vivo* studies (Latin for “in life”), so that the alternative method provides an equivalent level of safety. The results of these studies are submitted for evaluation to the responsible scientific committee of EURL ECVAM, the European Union Reference Laboratory for alternatives to animal testing. Once the scientific validity of the method has been recognized by EURL ECVAM, the Organisation for Economic Co-operation and Development (OECD) can then officially accept the alternative method and incorporate it into an OECD Guideline.

Our activities and the legal framework

Cooperation with external partners – development, validation and acceptance of alternative test methods

Henkel actively promotes and participates in cross-industry programs for developing non-animal test methods. We are a (founding) member of the European Partnership for Alternative Approaches to Animal Testing (EPAA, see below) and of various committees of the European cosmetics association (Cosmetics Europe) focusing on alternatives to animal testing. Together with the EU Commission, the cosmetics industry has launched a EUR 50 million research program (SEURAT, http://www.seurat-1.eu/) to develop alternative methods for especially complex toxicological effects. In addition, we collaborate with partner companies and governmental agencies in carrying out validation projects to smooth the way for official acceptance of newly developed methods. Through national associations, we also play a role in organizations that promote alternative methods, such as the German Foundation for the Promotion of Alternative and Complementary Methods to Reduce Animal Testing (SET, http://www.stiftung-set.de/index.php?id=3&L=1), and represent the cosmetics industry on the Commission of the German Centre for Documentation and Evaluation of Alternatives to Animal Experiments (ZEBET, http://www.bfr.bund.de/en/zebet_database_on_alternatives_to_animal_experiments_on_the_internet__animalt_zebet_-1508.html).

European Partnership for Alternative Approaches to Animal Testing:

In November 2005, the European Partnership for Alternative Approaches to Animal Testing (EPAA, http://ec.europa.eu/enterprise/epaa/index_en.htm) was founded in Brussels as a joint initiative between the European Commission, European trade associations and companies, including Henkel, from seven industry sectors. The objective of the partnership is to accelerate the development, validation and acceptance of alternative approaches to animal testing.

In the Brussels 3Rs Declaration, the partners committed to replace, reduce and refine animal testing. Based on a joint action program, the participating parties not only collaborate to develop alternative methods but also devise new test strategies and evaluation concepts. The progress made has been announced in an annual report since 2006. As a founding member, we have been actively involved in the EPAA action program ever since it was launched.

Legal requirements in the European Union

Under the EU Cosmetics Regulation, cosmetic products have to comply with especially high standards of compatibility for consumers. Following the EU-wide ban of animal testing for **finished cosmetic products** in 2004, this ban was extended to **cosmetic ingredients** as well in 2009. Under the 7th Amendment to the EU Cosmetics Regulation dated February 27, 2003, animal testing of cosmetic ingredients has been banned in the EU since March 2009. The ban also applies to the marketing of cosmetic products if their ingredients have been tested on animals in order to meet EU cosmetics legislation requirements. There are only three safety aspects, known as end points, for which an exception was made until March 11, 2013, provided the animal tests for the relevant ingredient were performed outside the EU. For safety tests covering complex metabolic processes, such as carcinogenicity, chronic toxicity, reproduction toxicity, and sensitization, there are still no alternative methods capable of providing sufficiently conclusive results. However, certain possible methods are already in the validation phase.

With its chemicals legislation REACH, the European Union now requires all chemicals to be newly registered, evaluated and – where necessary – authorized (REACH = **R**egistration, **E**valuation, and **A**uthorization of **Ch**emicals). To make sure that this registration process does not lead to a significant increase in the number of tests on animals, suitable alternative methods must soon be made available and officially accepted.

Global approaches are essential:

In addition to the important cooperations within the EU, further efforts are necessary in order to ensure that alternative methods will be successfully implemented worldwide. To this end, Henkel and its partners are collaborating with scientists and regulatory bodies in various regions – through the EPAA, for example, which has been taking an increasingly international perspective since 2012. (http://ec.europa.eu/enterprise/epaa/3_2_conf_2012.htm).

Credits

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